Drug interaction between erlotinib and phenytoin for brain metastases in a patient with nonsmall cell lung cancer

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Drug interaction between erlotinib and phenytoin for brain metastases in a patient with non-small cell lung cancer

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Abstract

Erlotinib, a substrate drug metabolized by the CYP3A4 enzyme, is an epidermal growth factor receptor tyrosine kinase inhibitor used to treat non-small cell lung cancer (NSCLC). Concomitant use of erlotinib and the antiepileptic drug phenytoin, an inducer of CYP3A4, may result in a drug-drug interaction accompanied by changes in the blood concentrations of both drugs. We determined the blood concentration of each drug to confirm the interaction between phenytoin and erlotinib in a case of NSCLC with brain metastases. The phenytoin blood concentration (8.2–10.0 μg/mL) gradually increased 3-fold (to 24.2 μg/mL) 7 months after the start of erlotinib (150 mg/d) co-administration. The erlotinib blood concentration which was maintained at 0.15–0.37 μg/mL under phenytoin co-administration, increased 12-fold (to 1.77 μg/mL) after the stoppage of phenytoin co-administration. The present case revealed that blood phenytoin increased and blood erlotinib decreased subsequent to the interaction of the 2 drugs in the CYP3A4 metabolic enzyme system.

Keywords: drug-drug interaction, erlotinib, phenytoin

1. Introduction

Erlotinib, a substrate drug metabolized by the CYP3A4 enzyme, is an epidermal growth factor receptor tyrosine kinase inhibitor used to treat advanced or metastatic non-small cell lung cancer (NSCLC) [1-3]. Erlotinib was sometimes used concomitantly with the antiepileptic drugs phenytoin, carbamazepine, or valproic acid in NSCLC patients with convulsions due to brain metastases [4,5]. A case report on the interaction between erlotinib and phenytoin showed that blood phenytoin levels increased after the start of erlotinib co-administration [6]. This interaction may be due to the inhibitory effects of erlotinib on phenytoin metabolism in the CYP system [6]. However, whether change in blood erlotinib levels occurs in this drug–drug interaction remains unclear, although a change in erlotinib metabolism by CYP3A4 during co-administration of phenytoin, a strong CYP inducer, is speculated [6].

In the present case report, we determined phenytoin and erlotinib blood concentrations to confirm the clinical impact of the interaction of these 2 drugs in an NSCLC patient with brain metastases. The study was approved by the ethics committee of Ibaraki Prefectural Central Hospital (approval no: 26-4; dated April 23, 2014), and informed consent was obtained from the patient.

2. Case report

A 59-year-old woman was diagnosed as having adenocarcinoma of the left upper lung lobe in July 2010. She underwent surgery and received adjuvant chemotherapy of cisplatin plus docetaxel (4 cycles) and S-1 (17 cycles). Two years later, she presented with convulsive seizures due to brain metastases and was started on phenytoin administration (180 mg/d). She received craniotomy for tumor resection and gefitinib administration (250 mg/d) in November 2012. Three months later, a reduction in the dose of gefitinib to administration every other day was required because of liver dysfunction. Then, the brain metastases recurred, as did the convulsive seizures, which required levetiracetam administration in addition to phenytoin. Gefitinib was switched to erlotinib (150 mg/d) in October 2014 because of tumor progression.

The phenytoin blood concentration, which was maintained at 8.2–10.0 μg/mL during gefitinib treatment, increased to 24.2 μg/mL 7 months after the switch to erlotinib (Fig. 1). Phenytoin was stopped because of nystagmus, a phenytoin toxicity symptom due to high concentrations of the drug in blood. The erlotinib blood concentration was maintained at 0.15–0.37 μg/mL during the 7-month phenytoin co-administration. The erlotinib blood concentration gradually increased after phenytoin co-administration was stopped and reached 1.77 μg/mL under the unchanged daily dose of erlotinib (Fig. 1) and

liver and kidney functions.

3. Discussion

This is the first case report describing change in blood drug concentrations due to an interaction between phenytoin and erlotinib, in which the concentration of phenytoin increased and that of erlotinib decreased during concomitant use of the drugs for NSCLC with brain metastases.

The change in phenytoin blood concentration, which was increased by erlotinib co-administration, is similar to that previously described by Grenader at al [6]. They reported that phenytoin concentrations increased 4-fold, from 5.9–7.2 μg/mL at baseline to 13.5–25.3 μg/mL, under erlotinib co-administration [6]. The present case showed a similar elevation of phenytoin concentration, from 8.2–10.0 μg/mL at baseline to 16.1–24.2 μg/mL under erlotinib co-administration (Fig. 1). Both cases showed toxic symptoms of phenytoin—nystagmus, diplopia, and unsteady gait—when the blood concentration exceeded the therapeutic range of phenytoin, ie, 10–20 μg/mL. This elevation of phenytoin blood concentration may be caused by the inhibitory effects of erlotinib on metabolism or by excretion of phenytoin.

Since erlotinib is metabolized by CYP3A4 [7], change in CYP3A4 activity, including that

induced by drug-drug interaction, may cause the change in erlotinib blood concentration. Systemic exposure to erlotinib was reported to be increased by 86% and decreased by 69% when the CYP3A4 inhibitor, ketoconazole [8], and inducer, rifampicin [9], were co-administered, respectively. Phenytoin, an inducer of CYP3A4, is known to provide drug interactions with CYP3A4 substrates including chemotherapeutic agents [10]. The present case also confirmed a reduction in erlotinib concentration of 79% to 92% during phenytoin co-administration. The erlotinib concentration, which was as low as 0.15–0.37 μg/mL under phenytoin co-administration increased approximately 12-fold (to 1.77 μg/mL) after stoppage of phenytoin, which corresponded to the change in erlotinib clearance from 41.7 to 3.53 L/h. The erlotinib clearance under phenytoin co-administration (41.7 L/h) was extremely high (10-fold higher) when compared with previously reported values ranging from 4.14 to 5.43 L/h [11]. Thus, interaction between phenytoin and erlotinib may increase erlotinib clearance, resulting in reduction in erlotinib exposure in addition to increase in phenytoin exposure.

Reduction in erlotinib exposure failed to inhibit the progression of brain metastases, which was confirmed by change in the tumor size as assessed by magnetic resonance imaging (data not shown). Erlotinib blood concentration under phenytoin co-administration was extremely low when compared with those of a phase II trial [11]

and seemed to be insufficient for treating brain metastases. The present case, therefore, showed rapid progression of the brain metastases despite the switch from gefitinib to erlotinib.

When using concomitant phenytoin and erlotinib, physicians should pay attention to possible drug–drug interactions inducing unfavorable effects from both drugs—toxic symptoms in the case of phenytoin and insufficient antitumor effects in the case of erlotinib, though the combination is not contraindicated. Therapeutic drug monitoring for phenytoin and erlotinib is recommended to optimize the relevant dose amounts when patients require concomitant use of both drugs.

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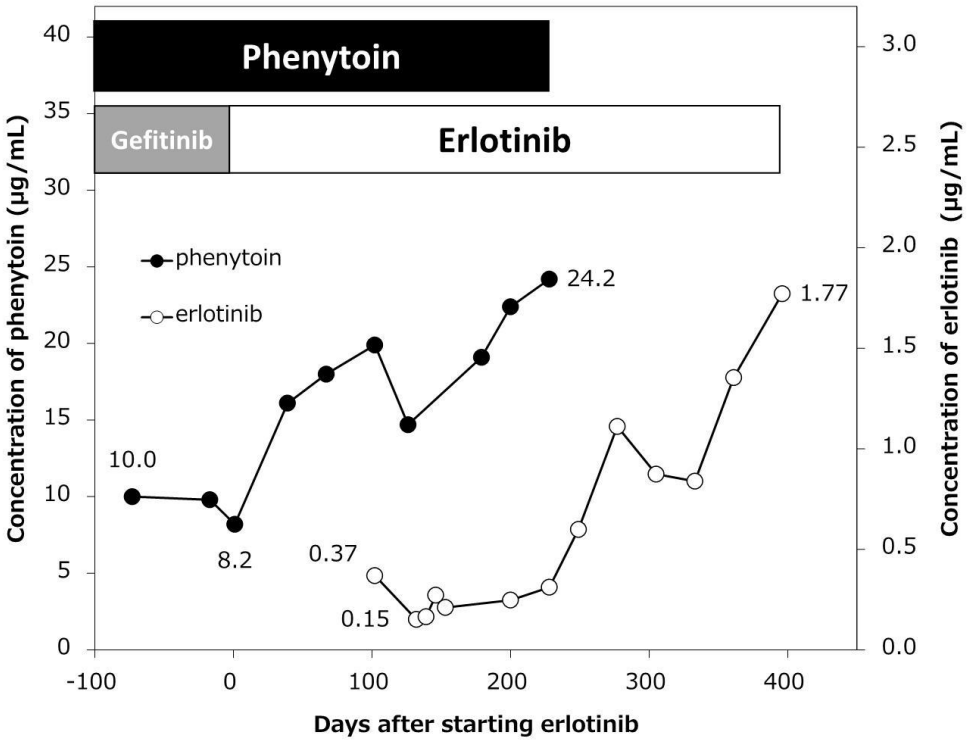
Figure legend

Figure 1. Blood concentrations of phenytoin and erlotinib.

Figure 1


Phenytoin
Gefitinib
Erlotinib
phenytoin
erlotinib
24.2
1.77
10.0
8.2
0.37
0.15
Concentration of phenytoin (μg/mL)
Concentration of erlotinib (μg/mL)
Days after starting erlotinib
40
35
30
25
20
15
10
5
0
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-100
0
100
200
300
400